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2005-1025

IN THE U.S. PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re application of	Appeal No.
Willem VAN DIJK et al.	Conf. 9012
Application No. 10/500,390	Group 1655
Filed September 14, 2004	Examiner C. CHEN

NEGATIVELY CHARGED POLYSACCHARIDE
DERIVABLE FROM ALOE VERA

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MAY IT PLEASE YOUR HONORS:

(i) Real Party in Interest

The real party in interest in this appeal is the assignee, BIOCLIN B.V. of Delft, the Netherlands.

(ii) Related Appeals and Interferences

None.

(iii) Status of Claims

Claims 27-29, 31-44, 48-50, 52 remain in this application.

Claims 31-34, 38 and 40 remain withdrawn.

Claims 1-26, 30, 45-47 and 51 have been cancelled.

This appeal is taken from the final rejection of claims 27-29, 35-37, 39, 41-44, 48-50, 52.

(iv) Status of Amendments

The claims, which have been last amended in the Amendment filed concurrently with this brief, are set forth in the Claims Appendix.

(v) Summary of the Claimed Subject Matter

The claimed subject matter is drawn a composition defined in two independent claims:

Claim 27 describes a composition, consisting essentially of:

isolated polysaccharides derived from Aloe vera wherein:

(Specification page 2, lines 20-21 in light of lines 15-16; table 1 for the "consisting essentially of" language.)

a) the polysaccharides comprise 60-90% D-mannose, 30-10 % D-glucose and 0-10 % other monosaccharides and the ratio of D-mannose and D-glucose in said polysaccharide is about 5:1 to 20:1;

(Specification page 2, lines 22-24 and page 3 lines 3-4.)

b) the polysaccharides are negatively charged;

(Specification page 2, lines 15-16 and 24)

c) the polysaccharides bind to a positively charged column; and

(Specification page 2, lines 24-25.)

d) the polysaccharides have an average molecular weight higher than 50 kD.

(Specification page 2, line 30 to page 3, line 1.)

Claim 52 describes a composition, consisting of:

an isolated, negatively-charged polysaccharides fraction from Aloe vera, the fraction being able to bind to a positively charged column, wherein

(Specification page 2, lines 15-16, 20-21, and 24-25)

the polysaccharides comprise 70 - 90 % D-mannose, 30-10% D-glucose and 0-10% other monosaccharides,

(Specification page 2, lines 21-24)

the ratio of D-mannose and D-glucose in the polysaccharides is about 5:1 - 20:1, and

(Specification page 2, lines 22-24 and page 3 lines 3-4.)

the polysaccharides have an average molecular weight of about 100-300 kD.

(Specification page 2, lines 30-31.)

(vi) **Ground of Rejection to be Reviewed on Appeal**

Whether claims 27-29, 35-37, 39, 41-44, 48-50 and 52 would have been obvious, within the meaning of 35 U.S.C. § 103(a) over QIU et al. U.S. 6,133,440 (QIU) in view of STRICKLAND et al. U.S. 5,824,659 (STRICKLAND), YARON et al. J. Agric. Food Chem 1992 (YARON), VILKAS et al. 1986, Biochimie, 68: 1123-1127(VILKAS) and SHAND et al. U.S. 5,902,796 (SHAND).

(vii) Arguments

None of claims 27-29, 35-37, 39, 41-44, 48-50, and 52 is obvious.

The claims are rejected separately according to the subheadings below.

Claims 27-29

Independent claim 27 is directed to a composition that consists essentially of isolated, negatively charged polysaccharides derived from Aloe Vera, which bind to a positively charged column.

QIU formed the basis of the rejection. QIU discloses an active and isolated mixture of polysaccharides from Aloe. These polysaccharides, referred to as Immuno-10, have a purity of greater than 95% compare (as described in column 5, lines 23-43) to claim 27 as shown in the table below:

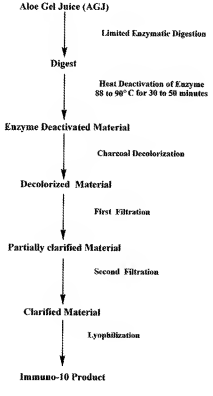
Property	*Claim 27*	*QIU*
Average Molecular weight (kDa)	Greater than 50	70-80 (range 50-200)
% of D-mannose	60-90%	90%
% of D-glucose	30-10%	5% or less
Ratio of D-mannose to D-glucose	5:1 to 20:1	Not specified. At best, suggests 18:1 to greater than 20:1
% of other monosaccharides	0 to 10%	5% or less (of D-galactose)

As seen in the above table, QIU does not disclose 30-10% D-glucose. While the claimed ratio of D-mannose and D-glucose is not specifically disclose, QIU, at best, suggests a ratio of 18:1 to ratios "greater than 20": 1.

QIU also fails to suggest that the polysaccharides bind to a positively charged column, or that the polysaccharides are negatively charged.

Indeed, QIU does not require a separation step, except for the purpose of decolorization.

The method of QIU involves subjecting the total polysaccharides in Aloe gel juice to enzymatic hydrolysis, and the optional filtering is for decolorization of the hydrolyzed product (Column 2, lines 50-62), e.g., as shown in Figure 1:



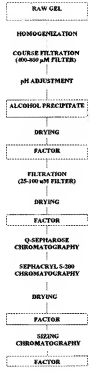
QIU explains that an advantage of this method is that one obtains a much higher and more stable activity than native Aloe gel extracts, i.e., one is able to preserve the immunomodulatory activity of Aloe (Column 2, lines 21-31 and 43-50). This is in contrast to the prior art methods, which, due to lengthy 4-24 hour alcohol precipitation and centrifugation steps fail to preserve immunomodulatory activity of Aloe (column 2, lines 29-40 and abstract). Moreover, QIU asserts that the method is faster, simpler, more amenable to scale-up, carried out without organic solvents, and able to increase solubility for use as an oral or topical formulation for the restoration or stimulation of the human immune system (Column 3, lines 7-21).

SHAND was offered for teaching isolating bioactive material from Aloe Vera using a positively charged column.

However, SHAND merely discusses the technique in the broadest manner. SHAND does not recognize that fractions from plant or animal extracts that are obtained after elution from a positively charged DEAE column showed good curative properties. These fractions particularly comprise the polysaccharides in a negatively charged form. Appellant shows in comparative studies by (see e.g. table 1 of the application) that these negatively charged polysaccharides ($I\text{-}D_T$) demonstrated high inhibiting characteristics compared to said polysaccharide fractions ($I\text{-}D_0$) that do not bind to the positively charged column.

The Examiner's position was that it would have been obvious to use a positively charged column because "aloe vera bioactive factor needs proper processing with positively charged column as taught by Shand et al."

However, SHAND does not simply utilize a positively charged column. This type of chromatography is used in addition to multiple steps. Indeed, SHAND suggests alcohol precipitation and includes lengthy centrifugation within the range of 10 minutes to 48 hours, contrary to the objective of QIU. Furthermore, SHAND seeks to obtain only a fraction (i.e., "factor")of the bioactive components (e.g. Figures 2, 5, 8-11 and 16). Figure 8 shows the use of such a positively charged column Q-Sepharaose:



Furthermore, SHAND fails to suggest that use of such a separation technique produces a composition comprising negatively charged polysaccharides, and SHAND fails to suggest that negatively charged fractions show promising properties.

Thus, one of ordinary skill in the art would have been strongly discouraged from even considering SHAND for improving the bioactive content of QIU, given the fact that negatively charged fractions are not identified as being advantageous and the use of a positively charged column remove specific bioactive factors, i.e., not all of the bioactive material are collected as required by QIU (e.g., note the "factors" in the Figures of SHAND).

This is contrary to the method of QIU in which the entire polysaccharide composition is required. As noted previously, the optional filtration in QIU is used to clarify the composition, not to isolate specific bioactive factors (See, e.g., column 2, lines 50-62 and Figure 1 of QIU).

Indeed, as evidenced by table 1 of the present application, mannose and glucose as such are not necessarily negatively charged, and, hence, they will not bind to a positive column. Fraction I-D_2, which mainly comprises mannose and glucose, does not bind to a positively charged column. See, e.g., line 9 page 9 to line 17, page 10 of the specification.

Thus, one would have expected that the use of a positively charge column would have rendered the composition of

QIU less effective due to the isolation of only a fraction of the bioactive content.

If proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984)

Consequently, there would have been no suggestion to use the positively charge column of SHAND to obtain the polysaccharides mixture of QIU, and SHAND does not remedy the shortcomings of QIU for reference purposes.

In support of the conclusion of obviousness, the Examiner offered STRICKLAND, YARON and VILKAS as evidence that one of ordinary skill in the art would have had a reasonable expectation of success in obtaining the claimed composition based on the modification of QIU in view of SHAND.

However, these documents fail to suggest a reasonable expectation of success.

STRICKLAND also fails disclose that the polysaccharides comprise 10 - 30 %D-glucose, and that the polysaccharides are negatively charged and bind to a positively charged column. STRICKLAND also fails to disclose or suggest to specifically isolating negatively charged polysaccharides.

YARON describes an Aloe Vera gel (in Table 1) having only 0.2% polysaccharides (QIU includes greater than 95%)with a

lower mannose level (e.g., 60.2% mannose) and a much higher glucose level (e.g., 22.2% glucose). Indeed, YARON, at best, suggests a mannose:glucose ratio of 3:1. YARON does not teach isolating the negatively charged polysaccharides, as claimed and proposed by the combination of QIU and SHAND. Consequently, YARON shares very little with the proposed combination.

Although VILKAS does teach a ratio of mannose to glucose, VILKAS is only concerned with an isolated fraction isolated from Aloe and filtered by a positively charged column (i.e., DEAE anion exchange column). Thus, VILKAS does not look at the entire active polysaccharide composition as required by QIU, but only a fraction, and there is no suggestion that one could still achieve the desired immunomodulatory activity of QIU with only a fraction of the polysaccharides.

The Examiner further asserted that the "claimed amounts were well within the purview of the ordinary artisan at the time the invention was made in an effort to optimize the desired result" (second to last paragraph on page 6).

A particular parameter must first be recognized as a result-effective variable, i.e., a variable which achieves a recognized result, before the determination of the optimum or workable ranges of said variable might be characterized as routine experimentation. *In re Antonie*, 559 F.2d 618, 195 USPQ 6 (CCPA 1977). As noted above, none of STRICKLAND, YARON and VILKAS teaches the same composition and/or a method similar to

QIU or QIU modified by SHAND. Thus, there is no variable within the method of QIU (with or without SHAND) as being a result-effective variable to adjust the level of glucose to approach that of the claimed invention without negatively impacting the ratio of mannose to galactose as desired by QIU, or the level of mannose. Indeed, QIU is more concerned with the ratio of galactose to mannose than the presence of glucose, e.g., for the purpose of pharmaceutical grade polysaccharides (Column 5, lines 34-42).

Therefore, the proposed combination does not render obvious independent claim 27, and dependent claims 28 and 29, and the rejection should be reversed.

Claims 35-37

Claim 35, from which claims 36 and 37 depend, concerns a plant or animal NAG-25 extract comprising the composition according to claim 27.

None of the documents teaches or suggests the composition of claim 27, as noted above relative claim 27. Thus, the combination cannot teach a plant or animal NAG-25 extract comprising the claimed composition.

Therefore, the proposed combination does not render obvious claims 35, 36 and 37, and the rejection should be reversed.

Claim 39

Claim 39 concerns an ultrafiltration aloe extract comprising the composition according to claim 27.

As the combination fails to suggest the composition of claim 27, the combination fails to suggest an ultrafiltration product with the same features as recited.

Therefore, the proposed combination does not render obvious claim 39 and the rejection should be reversed.

Claim 41

Claim 41 concerns a food supplement or dietary food, comprising the composition according to claim 27.

QIU discloses a product which may be used in an oral dosage.

SHAND was offered for suggesting a food supplement or dietary food.

As the combination fails to suggest the composition of claim 27, the combination fails to suggest a food supplement or a dietary food comprising the composition according to claim 27.

Therefore, the proposed combination does not render obvious claim 41, and the rejection should be reversed.

Claim 42

Claim 42 is directed to a cosmetic product comprising the composition according to claim 27.

As noted above relative to claim 27, the proposed combination fails to teach the composition of claim 27. Thus, the combination fails to suggest a cosmetic according to claim 42.

Therefore, the proposed combination does not render obvious claim 42, and the rejection should be reversed.

Claim 43

Claim 43 is directed to a pharmaceutical composition comprising the composition according to claim 27.

The proposed combination fails to teach the various features of claim 27 for the reasons discussed above.

Indeed, in order to even approach the claimed invention, would have been contrary to the "pharmaceutical grade" product disclosed by QIU. QIU discloses that the Pharmaceutical grade of the polysaccharides contains mainly D-galactose, i.e., not 10-30% glucose as claimed, and D-mannose, and their ratio should be 1 to 9.6 +/- 2.2, compared to the "basic" grade, which is closer to the claimed invention, e.g., 90% D-mannose, 5% or less of D-glucose, 5% or less of D-galactose. See, e.g., Column 5, lines 34-42 of QIU.

Thus, in order to approach the claimed pharmaceutical composition, one would have had been forced to increase the level of D-glucose far beyond the pharmaceutical grade accepted by QIU, and, accordingly, rendered the composition unsatisfactory for the pharmaceutical use by QIU.

Therefore, the proposed combination does not render obvious claim 43 and the rejection should be reversed.

Claim 44

An anti-bacterial, anti-viral or anti-inflammatory pharmaceutical comprising the composition according to claim 27.

The proposed combination fails to teach the various features of claim 27 for the reasons discussed above.

The "pharmaceutical grade" polysaccharides disclosed by QIU contain mainly D-galactose, i.e., not 10-30% glucose as claimed, and D-mannose, and their ratio should be 1 to 9.6 +/- 2.2, compared to the "basic" grade, which is closer to the claimed invention, e.g., 90% D-mannose, 5% or less of D-glucose, 5% or less of D-galactose (Column 5, lines 34-42 of QIU).

Thus, in order to approach the claimed pharmaceutical, one would have had been forced to increase the level of D-glucose far beyond the pharmaceutical grade accepted by QIU, and, accordingly, rendered the composition unsatisfactory for the pharmaceutical use by QIU.

Therefore, the proposed combination does not render obvious claim 44 and the rejection should be reversed.

Claim 48

Claim 48 is directed to an oral dosage form selected from the group consisting of tablet, capsule and syrup comprising the composition according to claim 27.

As noted above, the proposed combination fails to suggest a composition according to claim 27, and, thus, the combination fails to suggest the claimed oral dosage.

Indeed, QIU discloses an oral dosage for pharmaceutical use. The "pharmaceutical grade" of polysaccharides disclosed by QIU, however, contain mainly D-galactose, i.e., not 10-30% glucose as claimed, and D-mannose, and their ratio should be 1 to 9.6 +/- 2.2, compared to the "basic" grade, which is closer to the claimed invention, e.g., 90% D-mannose, 5% or less of D-glucose, 5% or less of D-galactose. See, e.g., Column 5, lines 34-42 of QIU.

Thus, in order to approach the claimed oral dosage, one would have had been forced to increase the level of D-glucose far beyond the pharmaceutical grade accepted by QIU, and, accordingly, rendered the composition unsatisfactory for the pharmaceutically-acceptable oral use by QIU.

Therefore, the proposed combination does not render obvious claim 48 and the rejection should be reversed.

Claim 49

Claim 49 is directed to topical dosage form selected from the group consisting of cream and gel comprising the composition according to claim 27.

The proposed combination fails to teach the various features of claim 27 for the reasons discussed above.

Although QIU does teach a topical dosage, the "pharmaceutical grade" of polysaccharides disclosed by QIU contain mainly D-galactose, i.e., not 10-30% glucose as claimed, and D-mannose, and their ratio should be 1 to 9.6 +/- 2.2, compared to the "basic" grade, which is closer to the claimed invention, e.g., 90% D-mannose, 5% or less of D-glucose, 5% or less of D-galactose. See, e.g., Column 5, lines 34-42 of QIU.

Thus, in order to approach the claimed topical dosage, one would have had been forced to increase the level of D-glucose far beyond the pharmaceutical grade accepted by QIU, and, accordingly, rendered the composition unsatisfactory for the pharmaceutically-acceptable topical use by QIU.

Therefore, the proposed combination does not render obvious claim 49 and the rejection should be reversed.

Claim 50

Claim 50 is directed to an injectable dosage comprising the composition according to claim 27.

The proposed combination fails to teach the various features of claim 27 for the reasons discussed above.

QIU discloses both a basic grade and pharmaceutical grade of polysaccharides, and one of ordinary skill in the art would have been prompted to select a pharmaceutical grade for an injectable dosage. The pharmaceutical grade of the polysaccharides of QIU, however, contains mainly D-galactose and D-mannose in a ratio of 1 to 9.6 +/- 2.2, compared to the "basic" grade 90% D-mannose, 5% or less of D-glucose, 5% or less of D-galactose. As this "basic" grade includes less than the claimed amount of D-glucose or the corresponding ratio of D-glucose to mannose, the "pharmaceutical" grade would have been even further from the claimed invention.

Thus, in order to approach the claimed injectable dosages, one would have had been forced to increase the level of D-glucose far beyond the acceptable level for pharmaceutical grade, and, accordingly, rendered the composition unsatisfactory for a pharmaceutical uses such as injectable dosages.

Therefore, the proposed combination does not render obvious claim 49 and the rejection should be reversed.

Claim 52

Claim 52 is directed to a composition including isolated, negatively-charged polysaccharides fraction from Aloe Vera, which binds to a positively charged column similar to claim

27. However, claim 52 differs in scope by reciting "consisting of" and a specific range of molecular weights for the composition.

QIU, SHAND, STRICKLAND, YARON and VILKAS were also applied against independent claim 52, but the features solely recited in claim 52 were not addressed.

The claimed invention and QIU are compared in the table below:

Property	***Claim 52***	***QIU***
Average Molecular weight (kDa)	**100-300**	**70-80 (range 50-200)**
% of D-mannose	**70-90%**	**90%**
% of D-glucose	**30-10%**	**5% or less**
Ratio of D-mannose to D-glucose	**5:1 to 20:1**	**Not specified. At best, suggests 18:1 to greater than 20:1**
% of other monosaccharides	**0 to 10%**	**5% or less (of D-galactose)**

Thus, in addition to failing to suggest that the polysaccharides bind to a positively charged column, the polysaccharides are negatively charged, and the D-glucose content of 30-10%, QIU also fails to disclose a composition consisting of an average molecular weight similar to that claimed.

Consequently, QIU, SHAND, STRICKLAND, YARON and VILKAS fail to render obvious claim 52 for all the reasons set forth above relative to claim 27.

As to the "consisting of" language and the average molecular weight of 100-300 kDa, QIU discloses an average molecular weight of 70-80 kDa with a range of 50-200 (Column 5, lines 27-33). In order to even approach the claimed invention, one would have been forced to discard the portion of the active polysaccharides that have small molecular weights, and possibly upset the ratio of D-glucose, D-galactose and D-mannose.

As one would have expected that a removal of active components from the composition of QIU would have negatively affected the activity of the composition desired by QIU, one would have been discouraged from making such a modification to the composition of QIU.

Thus, further to reasons provided above relative to claim 27, modification of QIU to obtain a composition "consisting of" an average molecular weight of 100-300 kDa would not have been obvious.

Therefore, the rejection of claim 52 should be reversed.

Conclusion

From the foregoing discussion, it is believed to be apparent that the rejections on appeal are improper and should be reversed. Such action is accordingly respectfully requested.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future submissions, to charge any underpayment or credit any overpayment to Deposit Account No. 25-0120 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17.

Respectfully submitted,

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Enclosures: Claims Appendix

(viii) Claims Appendix

27. A composition, consisting essentially of:

isolated polysaccharides derived from Aloe vera wherein:

a) the polysaccharides comprise 60-90% D-mannose, 30-10 % D-glucose and 0-10 % other monosaccharides and the ratio of D-mannose and D-glucose in said polysaccharide is about 5:1 to 20:1;

b) the polysaccharides are negatively charged;

c) the polysaccharides bind to a positively charged column; and

d) the polysaccharides have an average molecular weight higher than 50 kD.

28. The composition according to claim 27, wherein:

a) the polysaccharides comprise 70 - 90 % D-mannose, 30-10% D-glucose and 0-10% other monosaccharides

b) the polysaccharides are negatively charged

c) the polysaccharides bind to a positively charged column.

29. The composition according to claim 27, wherein said polysaccharides have an average molecular weight of about 100 - 300 kD.

31. (withdrawn) A process for preparing the composition according claim 27, comprising the following process steps:

a) subfractionating an Aloe vera extract in two fractions, one with an apparent molecular weight of > ± 5 kD, named subfraction I and one with an apparent molecular weight of < ± 5 kD

b) passing of subfraction I over a positively charged column

c) eluting the part of subfraction I bound to said column with a salt solution, resulting in subfraction I-DI

d) desalting and ultrafiltration of I-DI, and

e) optionally preparing subfractions of I-DI with desired apparent molecular weights of > 300 kD, 100 - 300 kD, 50 - 100 kD and 10 - 50 kD.

32. (withdrawn) The process according to claim 31 further comprising a pre purification step before process step a).

33. (withdrawn) The process according to claim 31 wherein a DEAE-Sephadex or DEAE-Sepharose column is used during process step b).

34. (withdrawn) The process according to claim 31 further comprising a step of sequential ultra filtration or preparative FPLC over a Superose column.

35. A plant or animal NAG-25 extract comprising the composition according to claim 27.

36. The plant or animal NAG-25 extract according to claim 35, wherein the extract is an aloe plant extract.

37. The plant or animal NAG-25 extract according to claim 36, wherein the extract is an aloe vera extract.

38. (withdrawn) A process for preparing a plant or animal NAG-25 extract according to claim 35, comprising applying a purification step of an untreated Aloe extract over a Sephadex G-25 column to remove materials with affinity for said column.

39. An ultrafiltration aloe extract comprising the composition according to claim 27.

40. (withdrawn) A process to prepare an Aloe ultra filter extract according to claim 39, comprising applying a step of ultra filtration to an Aloe extract.

41. A food supplement or dietary food, comprising the composition according to claim 27.

42. A cosmetic product comprising the composition according to claim 27.

43. A pharmaceutical composition comprising the composition according to claim 27.

44. An anti-bacterial, anti-viral or anti-inflammatory pharmaceutical comprising the composition according to claim 27.

48. An oral dosage form selected from the group consisting of tablet, capsule and syrup comprising the composition according to claim 27.

49. A topical dosage form selected from the group consisting of cream and gel comprising the composition according to claim 27.

50. An injectable dosage comprising the composition according to claim 27.

52. A composition, consisting of:

an isolated, negatively-charged polysaccharides fraction from Aloe vera, the fraction being able to bind to a positively charged column, wherein

the polysaccharides comprise 70 - 90 % D-mannose, 30-10% D-glucose and 0-10% other monosaccharides,

the ratio of D-mannose and D-glucose in the polysaccharides is about 5:1 - 20:1, and

the polysaccharides have an average molecular weight of about 100-300 kD.

(ix) Evidence Appendix

None.

(x) **Related Proceedings Appendix**

None.